SYNTHESIS OF SOME NEW THIENO[2,3-d]PYRIMIDIN-4-AMINE DERIVATIVES

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Abstract: Some new thieno[2,3-d]pyrimidin-4-amines have been prepared through base-catalyzed cyclocondensation reaction of 2-amino-4,5-dimethylthiophene-3-carbonitrile with aryl nitriles.
Keywords: 2-Amino-4,5-dimethylthiophene-3-carbonitrile; Aryl nitriles; Cyclocondensation; Thieno[2,3-d]pyrimidin-4-amines.

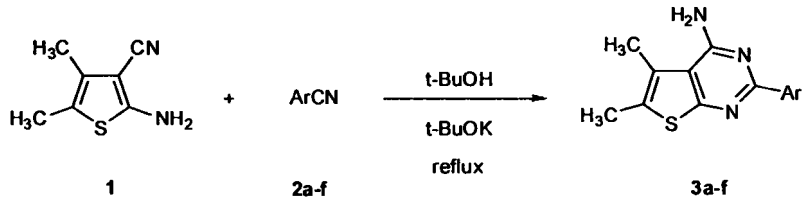
Introduction

Thieno[2,3-d]pyrimidines are a large group of heterocycles with diverse and interesting biological activities. These compounds are reported to possess significant analgesic,[1,2] fungicidal,[3] antibacterial,[4] antiviral[5] and antiinflammatory[6] activities. Also, some thieno[2,3-d] pyrimidines show CNS depressing activity[7] and are useful as muscle relaxants,[8] sedatives[8] diuretics,[9] pesticides and herbicides.[10] Various methods have already been proposed for the synthesis of these compounds and the most general ones involves cyclocondensation of suitably functionalized thiophenes with different electrophiles such as chloroformamidine,[11] α-substituted acetonitriles,[12] formic acid,[13] phosgen,[14] ethyl chloroformate[14] and guanidine.[15] To the best of our knowledge, cyclocondensation of 2-amino-4,5-dimethylthiophene-3-carbonitrile **1** with aryl nitriles for the synthesis of 2-aryl-5,6-dimethylthieno[2,3-d]pyrimidin-4-amines **3a-f** has not been reported in the literature.

Prompted by these findings and due to our interest in the synthesis of new heterocyclic compounds with potential biological activities[16-26] and in continuation of our work on the synthesis of new thieno[2,3-d]pyrimidine derivatives,[27-29] we report herein a convenient synthesis of some new 2-aryl-5,6-dimethylthieno[2,3-d]pyrimidin-4-amines **3a-f** that might be of pharmacological importance.

Results and Discussion

Cyclocondensation of 2-amino-4,5-dimethylthiophene-3-carbonitrile **1** with aryl nitriles **2a-f** in the presence of potassium t-butoxide in t-butanol under reflux gave products identified as 2-aryl-5,6-dimethylthieno[2,3-d]pyrimidin-4-amines **3a-f** (Scheme 1). The structural assignments of new compounds **3a-f** were based upon the spectral and microanalytical data. For example, the IR spectrum of **3a** was devoid of the stretching vibration band at 2191 cm^{-1} for CN absorption of the precursor.[30] Further proof came from the ^1H NMR spectrum which showed two singlet (δ 2.45 and 2.49 ppm) for methyl groups as well as a single broad band (δ 6.08 ppm) for NH_2 protons and the appearance of characteristic signals at δ 7.4-8.5 ppm for phenyl group. The MS of **3a** showed a molecular ion peak at m/z 255 (M^+) corresponding to the molecular formula $C_{14}H_{13}N_3S$. Also this compound gave satisfactory elemental analysis data.



1 2a-f 3a-f

a: Ar = Ph
b: Ar = 3-ClC_6H_4
c: Ar = 4-ClC_6H_4
d: Ar = 3-MeC_6H_4
e: Ar = 4-MeC_6H_4
f: Ar = 4-BrC_6H_4

Scheme 1

In conclusion, we have developed a facile method for the synthesis of new 2-aryl-5,6-dimethylthieno[2,3-d]pyrimidin-4-amines through base catalyzed cyclocondensation of 2-amino-4,5-dimethylthiophene-3-carbonitrile with aryl nitriles.

Experimental Section

Melting points were recorded on an Stuart Model SMP3 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. The ^1H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The mass spectra were determined on a Shimadzu GCMS 17A instrument. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer.

General procedure for the preparation of 2-aryl-5,6-dimethylthieno[2,3-d]pyrimidin-4-amines 3a-f

To a solution of the 2-amino-4,5-dimethylthiophene-3-carbonitrile **1** (5 mmol) and potassium *t*-butoxide (5 mmol) in *t*-butanol (25 mL), aryl nitriles **2a-f** (6 mmol) was added.The reaction mixture was heated under reflux for 6.0 hours. After the completion of the reaction (monitored by TLC, $CHCl_3$:MeOH, 95:5), the solvent was evaporated in vacuo, the residue was dissolved in water (15 mL) and subsequently neutralized by 1N HCl. The crude product was collected and recrystallized from ethanol/water to give compounds **3a-f** in 58-70% yields.

5,6-Dimethyl-2-phenylthieno[2,3-d]pyrimidin-4-amine (3a)

Yield 70%; mp 188-190 °C; ^1H NMR ($CDCl_3$) δ (ppm) 2.45 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 6.08 (s br, 2H, NH_2),7.4-8.5 (m, 5H, phenyl); IR (KBr disc) υ 3300, 3170 (NH_2) cm^{-1}; MS, *m/z*, M^+255; Anal. Calcd for $C_{14}H_{13}N_3S$: C, 65.85; H, 5.13; N, 16.46; S, 12.56. Found: C, 65.64; H, 5.29; N, 16.64; S, 12.42.

2-(3-Chlorophenyl)-5,6-dimethylthieno[2,3-d]pyrimidin-4-amine (3b)

Yield 58%; mp 233-235°C; ^1H NMR ($CDCl_3$) δ (ppm) 2.47 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 5.45 (s br, 2H, NH_2),7.3-8.5 (m, 4H, arom-H); IR (KBr disc) υ 3286, 3162 (NH_2) cm^{-1}; MS, m/z, M^+ 289, (M+2) 291; Anal. Calcd for $C_{14}H_{12}ClN_3S$: C, 58.03; H, 4.17; N, 14.50; S, 11.07. Found: C, 57.85; H, 4.03; N, 14.72; S, 10.91.

2-(4-Chlorophenyl)-5,6-dimethylthieno[2,3-d]pyrimidin-4-amine (3c)
Yield 63%; mp 219-222°C; ^{1}H NMR ($CDCl_3$) δ (ppm) 2.47 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 5.37 (s br, 2H, NH_2),7.4-8.5 (dd, 4H, arom-H); IR (KBr disc) υ 3277, 3149 (NH_2) cm^{-1}; MS, m/z, M^+ 289, (M+2) 291; Anal. Calcd for $C_{14}H_{12}ClN_3S$: C, 58.03; H, 4.17; N, 14.50; S, 11.07. Found: C, 58.17.; H, 4.08; N, 14.33; S, 11.19.

5,6-Dimethyl-2-(3-methylphenyl)thieno[2,3-d]pyrimidin-4-amine (3d)
Yield 60%; mp 201-203°C; ^{1}H NMR ($CDCl_3$), δ (ppm) 2.43 (s, 6H, $2CH_3$), 2.45 (s, 3H, CH_3), 5.45 (s br, 2H, NH_2), 7.3-8.3 (m, 4H, arom-H); IR (KBr disc) υ 3285, 3158 (NH_2) cm^{-1}; MS, m/z, M^+ 269; Anal. Calcd for $C_{15}H_{15}N_3S$: C, 66.88; H, 5.61; N, 15.60; S, 11.90. Found: C, 66.69; H, 5.77; N, 15.86; S, 11.74.

5,6-Dimethyl-2-(4-methylphenyl)thieno[2,3-d]pyrimidin-4-amine (3e)
Yield 64%; mp 220-222°C; ^{1}H NMR ($CDCl_3$) δ (ppm) 2.38 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 5.40 (s br, 2H, NH_2),7.3-8.4 (dd, 4H, arom-H); IR (KBr disc) υ 3282, 3157 (NH_2) cm^{-1}; MS, m/z, M^+ 269; Anal. Calcd for $C_{15}H_{15}N_3S$: C, 66.88; H, 5.61; N, 15.60; S, 11.90. Found: C, 67.11; H, 5.73; N, 15.35; S, 12.01.

2-(4-Bromophenyl)-5,6-dimethylthieno[2,3-d]pyrimidin-4-amine (3f)
Yield 62%; mp 231-233°C; ^{1}H NMR ($CDCl_3$) δ (ppm) 2.43 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 5.43 (s br, 2H, NH_2),7.5-8.4 (dd, 4H, arom-H); IR (KBr disc) υ 3280, 3149 (NH_2) cm^{-1}; MS, m/z, M^+ 333, (M+2) 335; Anal. Calcd for $C_{14}H_{12}BrN_3S$: C, 50.31; H, 3.62; N, 12.57; S, 9.59. Found: C, 50.12.; H, 3.77; N, 12.70; S, 9.48.

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